Molecular Links Between Alzheimer's Disease and Gastrointestinal Microbiota: Emphasis on Helicobacter pylori Infection Involvement

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Molecular links between Alzheimer's disease and Gastrointestinal microbiota: emphasis on *Helicobacter pylori* infection involvement

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease and main form of dementia, characterized by progressive cognitive decline and detrimental consequences in both personal-family and global level. Within this narrative review, we provide recent molecular aspects of Tau, a microtubule AD-associated protein as well as amyloid beta, involved in AD pathophysiology. Moreover, we provide additional emerging data from basic research as well as clinical studies indicating an implicating role of gastrointestinal microbiota (GI-M), including *Helicobacter pylori* infection (*Hp*-I), in AD pathophysiology. Likewise, we identify through a molecular prism the current evidence of AD pathogenesis as well as its linkage with GI-M and emphasizing the role of *Hp*-I. All in all, additional large-scale studies are required for the further clarification of AD pathophysiology and its connection with GI-M and *Hp*-I, so as novel therapies on molecular basis become available.

Introduction

Alzheimer's disease (AD) is the major cause of dementia characterized by the accumulation of amyloid beta (Aβ) protein, the hyperphosphorylation of tau protein, and neuroinflammation, thought to lead to neuronal loss and synaptic dysfunction (1). AD is estimated to affect worldwide approximately 46.8 million people over the age of 60, having a rising tendency (2–4); its incidence and prevalence rise exponentially with increasing age particularly in the western societies (5), except preventive strategies are developed (2). The predictions regarding the prevalence of the disease, led the World Health Organization (WHO) to describe AD as a “fast-growing epidemic” (6), as a result of its prediction that the number of affected people will triple by 2050 (7).

The economic consequences as well as the traumatic burden for both patients and caregivers are enormous. The outcome is fatal and patients develop with the time impaired cognition with parallel continuously deteriorated ability to carry out daily activities and onset of neuropsychiatric symptoms (8). The most characteristic symptom at the initial phase of the disease is the loss of short-term memory (9). During disease progression, the clinical manifestations are further expanded and include speaking problems, sudden changes in mood, depression and severe orientation problems (9,10). The later stages of AD are characterized by complete withdraw from family and social activities and finally, loss of body functions that ultimately lead to death. Importantly, the constantly increasing life expectancy due to major improvements in life quality and successful treatment of previously incurable diseases, represent a critical challenge for ageing-related syndromes (11). Especially for AD, there is a massive psychological as well as the mentioned economic burden for both patients and their families, which is reflected to the society (12).

Therefore, the utmost goal of the research community is to identify effective therapeutic strategies that do not only provide symptomatic relief (13), but also to intervene in the molecular mechanisms involved in the pathophysiology of this disease, that is complex and not yet fully elucidated. In the present narrative review, we aimed to provided new molecular

links between AD, gastrointestinal microbiota and *Helicobacter pylori* infection involved in the disease pathophysiology.

Alzheimer's disease and molecular data

AD typical histopathological findings include the extracellular senile plaque formation of amyloid-β peptide (Aβ) and the intracellularly accumulating Neurofibrillary Tangles (NFTs) of hyperphosphorylated tau (14).

Generally, regarding Aβ deposition involved in senile plaques formation (15), the proteolyctic cleavage of the Amyloid Precursor Protein (APP) by β- and γ-secretases leads to the formation of this small peptide (16,17), with its length ranging from 38- up to 43-amino acids. Even though the vast majority of the produced peptides have very fast turnover and are quickly degraded, the 42-amino acid long version ($A\beta_{42}$) is highly aggregation-prone and exhibits enhanced toxicity (18). Inside the amyloid plaques, Aβ is aggregated and thereby forming not only large fibrils, but also smaller insoluble oligomeric formations (19). Importantly, these amyloid plaques are usually surrounded by degenerating neurons and an increased number of activated microglia, thereby indicating an inflammatory response (20).

Likewise, regarding the implication of tau protein in AD etiology and progression, the intracellular deposition of hyperphosphorylated tau aggregates, leads to the formation of NFTs and Paired Helical Filaments (PHFs) (21,22).

Tau-related molecular data

Tau is a microtubule (MT)-associated protein involved in both the health and disease of neurons. In humans, the Microtubule Associated Protein tau gene (MAP) is transcribed predominantly throughout the Central Nervous System (CNS) and produces a long pre-mRNA that contains 16 exons (23). Specifically, six isoforms of tau are expressed predomi-

nantly in the CNS due to differences regarding the number of the 29-amino acid residue near the aminoterminal region (N-terminal projection domain) as well as in the presence of 3- or 4-repeat domains close to the carboxy-terminal insert (MT Binding Repeat Domain, RD) (24). Being the major functional role, the interaction of tau with the MTs is mediated through the electrostatic interactions between the positively charged RD and the negatively charged MT surface (25). The reduction of the tau-MT affinity is achieved through phosphorylation of tau, which under healthy conditions is a tightly regulated process (24,26).

The major hypothesis linking AD to the observed hyperphosphorylation in AD patients is the loss of this tight regulation for tau phosphorylation, which leads the protein to a higher phosphorylation state and consequently detaches from MTs and starts aggregating (27). This is mostly based on the observation that in PHFs from AD patients tau is found to be hyperphosphorylated in epitopes that are not present in healthy subjects (28–30). Even though tau can also be found to be hyperphosphorylated in conditions not related to AD (31), it is widely accepted that abnormal phosphorylation is a major (but not the exclusive) factor contributing to tau aggregation.

Patient-derived as well as *in vitro*-assembled tau filaments demonstrate the typical for amyloids cross-β structure (32,33), with the core consisting of about 90 amino acids within the RD region. As this part of the protein is also responsible for binding to MTs, tau aggregation and MT-interaction are considered as two mutually exclusive processes (34,35). Additionally, while the RD is the core of tau filaments, the N- and C-terminal parts are forming the characteristic “fuzzy coat” that surrounds the aggregation core (36,37).

The exact mechanism of tau-induced neurotoxicity remains unclear. A reasonable hypothesis is the loss of tau function due to hyperphosphorylation and aggregation. However, tau knockout mice do not demonstrate significantly overt phenotypes (38), most probably because other MAPs compensate the loss of tau function. Another proposed mechanism is the mislocalization of tau into post-synaptic spines and thereby leading to synaptic dysfunction (39). However, the most accepted scenario for the tau-mediated toxicity observed in AD is the gain of toxic function for the aggregated species. Even though initially the NFTs were

suggested to be the detrimental factor for the pathological phenotypes in neurons, there is growing evidence towards the significance of smaller oligomeric tau species. This is mostly based on the establishment of several experimental tau models that develop toxic phenotypes due to the presence of aggregates, but in the absence of fibrillar tau (40). However, the determination of the exact species responsible for the tau-induced toxic effects is extremely challenging, mostly due to the great complexity in preparation and assay read-out heterogeneity among several experimental efforts.

Additionally, the sequential deposition of aggregated tau species throughout the brain, combined with the elevated levels of tau in the cerebrospinal fluid (CSF) before AD symptoms occur (41), the affected brain areas, and the symptoms, led to the “tau spreading” hypothesis. According to this model, misfolded tau trans-cellularly spreads from initially affected brain areas even to long distant neuronal clusters (42), thereby propagating the disease-related pathology. This process has been recapitulated in murine systems through injection of patient-derived material or *in vitro* generated tau fibrils (43–46).

Specifically, the mentioned increased detection of tau in the CSF in various forms (full-length, differentially phosphorylated, cleaved etc.) is a well-established observation in AD (47). Since CSF-tau is also found in non-demented patients with acute brain injury or stroke (48), release of tau from cells was initially empirically interpreted as a result of cell death. However, the levels of phosphorylated or non-phosphorylated tau in the CSF of AD patients are reproducibly higher compared to adjusted controls with intact cognition (49–52) and the detection precedes the occurrence of the symptoms (41). Moreover, over the last years there has been a vast number of scientific studies regarding the active release of tau from cells (53) and it is firmly established that this occurs even in healthy neurons (54). These observations, combined with the “tau spreading” hypothesis as a determining factor for disease progression, eventually raised questions regarding a potentially active mechanism for tau secretion. As tau does not contain a signal peptide sequence, its secretion seems to follow other pathways, collectively referred to as “Unconventional Protein Secre-

tion" (UPS) (55,56) and more specifically the proposed pathways for tau are divided either in Type I or Type III UPS-dependent mechanisms (57–59).

Aβ- related data: infection hypothesis

Regarding Aβ and AD, although the implication in pathogenesis is well established, a previously thought causative relationship has been questioned; Aβ brain depletion therapies have mostly failed, thereby signifying further efforts to investigate novel mechanisms in order to clarify the pathophysiology of the disease and introduce new interventional and/or preventive strategies. In this respect, the "infection hypothesis" was recommended, though received little attention. Nevertheless, recent data indicate that Aβ is an antimicrobial peptide with broad-spectrum antimicrobial properties acting against bacteria, fungi, and viruses (60). Indeed, relative data indicate that microbial infections increase the synthesis of Aβ and the latter appears to be an innate immune defense antimicrobial peptide, which utilizes fibrillation to protect the host from variable pathogens. Moreover, brain infections often result in augmented amyloidogenic processing of the amyloid-β protein precursor and subsequent fibrillary aggregates of Aβ (61). The Aβ oligomers exhibit strong and broad-spectrum antimicrobial actions by inducing fibrils, which entrap infectious pathogens and disrupt cell membranes (62), while Aβ overexpression in experimental models leads to increased resistance to infection from viruses and bacteria (63,64). Therefore, the antimicrobial role of Aβ may explain why increased rates of infection have been observed in some of the AD clinical trials that depleted Aβ. Even though the Aβ production might be beneficial on the initial microbial challenge, potentially has gradually detrimental consequences as the infections turn to chronic and the host endeavors to remove the excess Aβ may reduce over time as a result of both microbial biofilm formation and microglial senescence (60,65). These data provide evidence to an infection hypothesis involved in AD pathophysiology.

B. Gastrointestinal microbiota including *Helicobacter pylori* and AD: molecular data

The gastrointestinal microbiota (GI-M) including *Helicobacter pylori* (*Hp*) and brain relationship is assumed as a potential pathogenic basis for neurological disorders of pronounced health impact such as AD (66,67); the GI-M-brain axis is critical for maintaining GI homeostasis and its dysregulation is involved in various disease states such as AD. Specifically, the GI-M is considered the principal reservoir of microbes in the human body, containing trillions of microbes and comprises the highest one among all microbial ecosystems, as it encodes approximately $4x10^6$ genes, which represents 150 times more the amount of human genes (68). The human GI-M as a vital endocrine "organ" is involved in important functions, such as influencing metabolism, inducing trophic and protective effects and instructing innate immunity (69). Moreover, several data highlight the role of the GI-M in the development of neurodegenerative diseases, and in particular AD; the contribution of GI-M dysbiosis (70) to the pathogenesis of AD is well depicted in animal models of AD (71,72). In this regard, there is a great deal of impetus for the complete understanding of the pathological function, genetic evidence and functional diversity of the GI-M that could result in AD development and the detection of relative risk factors (73).

Growing clinical evidence (74) discloses that the pathophysiology of several neurodegenerative disorders could depend on the GI-M and that the resident commensal microbiota influences neuroinflammation (75). In this regard, in a recent study, fecal samples from 43 AD patients and equal number of cognitive intact controls were collected. By using 16S ribosomal RNA sequencing technique, fecal microbiota composition was analyzed and was found to be different between the two groups; bacteria taxa such as *Bacteroides, Actinobacteria, Ruminococcus, Lachnospiraceae*, and *Selenomonadales* were different in AD patients from those in controls at taxonomic levels (76). Similar results revealed a study from Japan. Fecal samples from demented and non-demented patients were obtained, and the gut microbiome was assessed by terminal restriction fragment length polymorphism analysis. The

analysis disclosed differences in the composition of the gut microbiome; the number of *Bacteroides* (enterotype I) was lower and the number of 'other' bacteria (enterotype III) was higher in demented patients. Multivariable analyses demonstrated that the populations of enterotype I and enterotype III bacteria were both strongly associated with dementia, independent of the traditional dementia biomarkers (77). Other authors reported that gut microbiota (GM) of AD patients revealed decreased microbial diversity and is compositionally distinct from control participants. Moreover, they found phylum- through genus-wide differences in bacterial abundance such as decreased *Firmicutes*, increased *Bacteroidetes*, and decreased *Bifidobacterium* in the fecal microbiome of AD patients. Interestingly, the authors also observed correlations between levels of differentially abundant genera and CSF biomarkers of AD like Aβ42/Aβ40, phosphorylated tau (and their ratio) and chitinase-3-like protein 1 (78). Additional study demonstrated that the ammount of *Eubacterium rectale* and *Bacteroides fragilis* microorganisms in patients with amyloidosis were significantly reduced compared to the cognitive intact group, whereas the number of *Escherichia/Shigella bacteria* significantly increased, thereby supporting the notion that AD affects the GM (79). Furthermore, a large multicenter study revealed, that AD patients were characterized by significantly lower concentrations of cholic acid (primary bile acid) and increased levels of the bacterially produced deoxycholic acid (secondary bile acid) as well as of its conjugated forms. The increased deoxycholic to cholic acid ratio (reflection of 7α-dehydroxylation by GM), was strongly associated with cognitive incline (80). Likewise, rising evidence from epidemiologic studies and animal models links periodontitis, caused by oral microbiota with AD (81–83).

Focus on *Hp* infection (*Hp*-I), a study from France, assessed both clinical and biological data of 53 patients with AD, testing the suggestion that *Hp* could alter the cognitive status by increasing inflammation. Results showed a lower mini-mental state examination score ($p=0.017$), higher plasma interleukin (IL)-1β concentrations ($p=0.025$) and increased gastric atrophy ($p=0.020$) in infected participants compared to uninfected a higher cognitive impairment in *Hp*-positive AD patients (84). In cross-sectional study, by analyzing data from the US national health and nutrition examination survey, a group from US authors also investigated

the correlation between *Hp* positivity and cognitive performance among US adults. Results showed a poorer performance of *Hp*-positive 60-90 years old participants, regarding verbal memory test compared to negative. In addition, 20-59 years old infected non-Hispanic black and women performed worse on serial digits learning total errors compared to uninfected. This was a strong demonstration that *Hp* could, in some way, correlate with cerebral function even if its causative role is still to be established (85). Other authors, proposed that *Hp* could affect AD by interacting with Galectin-3, a glycan-binding protein implicated in several physiological and pathologic processes, including cell signaling, proliferation, and migration as well as in the stimulation of immune response (86).

Concerning GI-M proteins or metabolites, they might promote neurodegeneration either by inducing amyloid development through human proteins or by increasing inflammatory reactions to endogenous neuronal amyloids (87). The exposure to bacterial amyloid proteins in the GI tract may induce priming of the immune system and promote brain autoimmunity (88,89), thereby increasing the immune response to endogenous production of neuronal amyloids involved in neurodegeneration (75).

The human innate immune system recognizes bacterial amyloid proteins by introducing many signaling pathways (90), such as the toll like receptor (TLR) 1/2, Nod-like receptor-3 protein (NLRP3), transcriptional nuclear factor kappa-B (NF-κB), innate immune receptor CD14, and inducible nitric oxide synthase. Other misfolded proteins induced by bacteria can be involved in the tissue destruction and the production of pro-inflammatory cytokines connected with AD development (91), collectively indicating that there are interactions between brain protein misfolding and GI-M.

Disruption of the intestinal barrier (composed by mucus layer intestinal columnar epithelium and lamina propria) leads to translocation of bacteria (process known as atopobiosis) and toxic substances into the bloodstream associated with critically disorders; disruption of the intestinal barrier may induce local and systemic injuries playing a role in several disorders such GI tract and liver diseases, as well as in the aging process and in the systemic in-

flammatory response syndrome, including brain dysfunctions (92). In addition to alterations in the GM composition influencing gut permeability (93), the increased amount of bacteria in the small intestine also influences permeability, as seen in small intestinal bacterial overgrowth (SIBO) and some data indicate an increased SIBO prevalence in AD patients (94). In this respect, *Hp*-related disorders are also associated with dysmotility-induced gastrointestinal bacterial overgrowth (GIBO) that may lead to bacteremia with systemic complications including brain disorders (66). GM produces and secretes more than 100 metabolites, but their effects on the pathogenesis of AD has only began to be elucidated. Bacterial produced acids like (iso)valeric acid, (iso)butyric, propionic, acetic and formic acid have been studied and have been shown to affect the pathogenesis of AD by disturbing the activations of microglia and astrocyte, functioning inflammatory, and against aggregations of Ab and tau (95).

Some additional data indicate that the GI-M could disrupt the integrity of the blood-brain barrier (BBB) (96,97), thereby possibly contributing to brain pathologies. Additionally, GI-M dysbiosis could increase the production of lipopolysaccharides and pro-inflammatory cytokines that combined with the activation of T lymphocytes and monocytes have been suggested to induce augmented intestinal and BBB permeability. These effects have been directly linked to subsequent misfolded proteins increase, axonal injury and neuronal demyelination involved in the pathophysiology of AD (98).

Regarding the mentioned aberrantly phosphorylated tau playing a central role in AD pathophysiology (99), recent data indicate that GI-M-induced metabolite trimethylamine N-oxide (TMAO) is increased in the CSF of patients with AD and mild cognitive impairment (MCI) (69). Moreover, CSF TMAO concentrations are related with CSF biomarkers of AD pathology (phosphorylated tau and Aβ) and neuronal degeneration (total tau, neurogranin, and neurofilament light chain protein), offering supplementary support for the role of GI-M in AD pathophysiology. In this respect, a healthy diet seems to reduce the risk of AD development and experimental bioactive food ingestion appears to reduce neuroinflammation, oxidative

stress, Aβ aggregation, and tau hyperphosphorylation with a concomitant cognition improvement (100).

GI-M and *Hp* have been shown to affect neurodegenerative processes by promoting inflammation, inducing molecular mimicry mechanisms and cerebral accumulation of Aβ peptides. *Hp* is one of the identified bacterial pathogens in humans, which its role is principally as a pathogen or a commensal (101). *Hp*-I has been shown to influence GI-M composition, thereby promoting dysbiosis, which represents a potential significant topic for *Hp*-related GI pathologies and AD development (102–104).

In this respect, in a mouse model mimicking human AD, transgenic APP/PS1 mice were compared to wild-type histologically, microbiologically and behaviorally. The results showed impaired spatial learning and memory appeared in APP/PS1 mice, which was further aggravated 2 months later. The brain lesions were consistent immunohistochemically with amyloid plaques. Moreover, AD histological and behavioral manifestations in the APP/PS1 mice were found to be correlated with a specific GM state and microbiota diversity of APP/PS1 mice decreased with increased age; abundance of *Helicobacteraceae* and *Desulfovibrionaceae* at the family level and *Odoribacter* and *Helicobacter* at the genus level increased significantly in APP/PS1 mice than in WT mice, while *Prevotella* abundance in WT mice was significantly higher than in APP/PS1 mice (105). Moreover, two large-scale clinical surveys demonstrate that infectious burden, among others including *Hp,* is associated with worse cognitive performance in multiethnic cohort Northern Manhattan Studies (106,107). Moreover, regarding the impact of *Hp-I* on vascular dementia, *Hp* positive patients are characterized by higher pro-inflammatory cytokine levels (tumor necrosis factor (TNF)-α, IL-1β and IL-12) and worse scores of Montreal and Mini-Mental State Examination cognitive evaluations (108); the aforementioned pro-inflammatory cytokines appear to be involved in AD pathophysiology (109). Likewise, another recent study reported that *Hp* seropositivity is directly associated with incidence of all-cause and AD dementia and with AD mortality (110). Regarding the latter findings, by introducing the histologic analysis of gastric mucosa biopsy

for the documentation of active *Hp*-I, our own studies reported that *Hp* eradication regimen is associated with a lower 5-year mortality rate in AD patients (8). Comparable data are also obtained for glaucoma (defined as “ocular” AD) that shares similar risk factors and pathogenetic mechanisms with AD (111,112). Besides, two recent published review articles summarized additional substantial studies linking AD with *Hp* and GI-M (2,102). Three main mechanisms include the possibility of *Hp* to enter in the brain via the oral-, nasal-, olfactory-pathways or through the aforementioned disrupted BBB, thereby leading to neurodegeneration; a fourth mechanism includes the possibility of *Hp*-related toxic agents to access the brain via the GI tract fast retrograde neural pathway and thus inducing brain neurodegeneration pathologies (2). Other pathogens, which have been proven isolated in AD human brain, mostly in post mortem studies, include *Chlamydophila pneumoniae, Borrelia burgdorferi*, and other spirochetes or *herpes simplex virus type 1* (94).

Regarding the BBB dysfunction, inflammatory mediators including cytokines and chemokines produced by *Hp*-I, induce BBB disruption. For instance, *Hp*-I releases the mentioned TNF-α, acting at a distance and involving in BBB disruption via matrix metalloproteinases upregulation (2). Likewise, *Hp*-induced Vacuolating cytotoxin (VacA) displays chemotactic activities to the bone marrow-derived mast cells (BMDMCs) and stimulates BMDMCs to produce proinflammatory cytokines that damage the BBB (113). Beyond the activated mast cells releasing vascular endothelial growth factor (VEGF), IL-8, chymase, tryptase and mast cell growth factor connected to *Hp*-I, mast cells themselves release mediators including histamine, IL-8, tryptase, and VEGF, that disturb the BBB (114). Mast cell degranulation accelerates the secretion of these potent mediators, which can orchestrate neuroinflammation and affect the BBB integrity, thereby contributing to neurodegenerative processes (66).

Finally, regarding the mentioned phosphorylated tau involved in AD pathophysiology (99), *in vitro* and animal models verified that apart from $A\beta_{42}$, *Hp* induces tau hyperphosphorylation, which is directly linked to the AD-associated neurodegeneration. Specifically, incubation of *Hp* filtrated on mouse neuroblastoma N2a cells overexpressing AβPP caused an augmented production of presenilin-2 (a component of the γ- secretase enzyme complex in-

volved in the production of Aβ) and $A\beta_{42}$ (115). In the same study, intraperitoneal injection of *Hp* filtrate in rats induced spatial learning and memory deficits, abnormal hippocampal dendritic spine maturation, and augmented presenilin-2 and $A\beta_{42}$ in rat brain hippocampus and cortex. However, *Escherichia coli* filtrate injection did not influence cognitive function in rats and Aβ production in rats and cells (115). Moreover, *Hp* filtrate induced substantial tau hyperphosphorylation at several AD-related tau phosphorylation sites in mouse neuroblastoma N2a cells via activation of glycogen synthase kinase-3β (116). Equally, intraperitoneal injection of *Hp* filtrate in rats resulted in noteworthy tau hyperphosphorylation in hippocampal areas of rat brain, while microglial activation and raised brain/plasma cytokine levels were not observed. These studies appear to provide evidence of the association between *Hp*-I and AD-like Aβ and phospho-tau pathology, indicating that *Hp* eradication may be beneficial in the tauopathy prevention.

Collectively, viewing the aforementioned data, it seems that molecular data of GI-M and *Hp*-I may contribute to the pathophysiology of AD and thus further large-scale relative studies are necessary to elucidate this field.

C. Concluding remarks

AD is a global burden with rising tendency and affects mainly the elderly population. Since the consequences are disastrous for affected families and societies, the necessity of further investigation for elucidation of pathogenicity and development of novel therapies, is of enormous significance. Mechanistically, hallmarks of disease in CNS are regarded the extracellular amyloid plaque formation and tau protein hyperphosphorylation. The “infectious hypothesis” gains ground lately, since Aβ is considered as antimicrobial peptide. The GI-M, including *Hp* which its role is mainly as a pathogen or a commensal, through a plethora of emerging data from basic research as well clinical studies reinforce the aforementioned hypothesis; the interplay between brain and GI-M constitutes an axis, where immune and endocrine stimuli play a central key role for shaping homeostasis or leading to dysbiosis and

neurodegeneration. All in all, a new challenging era of understanding the complex patho-physiology of AD and impact of GI-M/*Hp* on neurodegeneration has just began. The future is expected to be exciting and further large-scale studies are warranted, so as a substantiation of our knowledge is achieved and novel etiologic therapies become available.

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